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CLINICAL THERAPEUTICS

Linezolid Population Pharmacokinetics in South African Adults with Drug-Resistant Tuberculosis

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ABSTRACT Linezolid is widely used for drug-resistant tuberculosis (DR-TB) but has a narrow therapeutic index. To inform dose optimization, we aimed to characterize the population pharmacokinetics of linezolid in South African participants with DR-TB and explore the effect of covariates, including HIV coinfection, on drug exposure. Data were obtained from pharmacokinetic substudies in a randomized controlled trial and an observational cohort study, both of which enrolled adults with drug-resistant pulmonary tuberculosis. Participants underwent intensive and sparse plasma sampling. We analyzed linezolid concentration data using nonlinear mixed-effects modeling and performed simulations to estimate attainment of putative efficacy and toxicity targets. A total of 124 participants provided 444 plasma samples; 116 were on the standard daily dose of 600 mg, while 19 had dose reduction to 300 mg due to adverse events. Sixty-one participants were female, 71 were HIV-positive, and their median weight was 56 kg (interquartile range [IQR], 50 to 63). In the final model, typical values for clearance and central volume were 3.57 liters/h and 40.2 liters, respectively. HIV coinfection had no significant effect on linezolid exposure. Simulations showed that 600-mg dosing achieved the efficacy target (area under the concentration-time curve for the free, unbound fraction of the drug [$fAUC_{0-24h}$]/minimal inhibitory concentration [MIC] $>$ 119 at a MIC level of 0.5 mg/liter) with 96% probability but had 56% probability of exceeding safety target (trough$h_{24h} > 2$mg/liter). The 300-mg dose did not achieve adequate efficacy exposures. Our model characterized population pharmacokinetics of linezolid in South African patients with DR-TB and supports the 600-mg daily dose with safety monitoring.

KEYWORDS modeling and simulation, NONMEM, optimized dosing regimen, popPK/PD, population pharmacokinetics, tuberculosis

Drug-resistant tuberculosis (DR-TB) continues to impede global efforts to control the tuberculosis epidemic. In 2019, there were an estimated 10 million new TB cases and half a million cases with rifampin-resistant TB (RR-TB), 78% of whom had multidrug-resistant TB (MDR-TB) (1–3). Until recently, only 54% of patients with DR-TB and only 30% of patients with extensive drug-resistant tuberculosis (XDR) achieved treatment success, but there has

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been marked improvement in outcomes with the introduction of effective new and repurposed antituberculosis agents (4).

Linezolid, the prototype member of the oxazolidinone antimicrobial class, has potent *in vitro* antituberculosis activity and is associated with improved treatment outcomes when added to multidrug regimens for DR-TB (5, 6). The World Health Organization recommends linezolid at a dose of 600 mg daily for most patients with RR-TB. Linezolid is associated with a high frequency of hematological and neurological adverse events, which appear to be dose- and duration-dependent, limiting its use in TB treatment (7, 8). Linezolid toxicity is due to structural homology between target 23S rRNA in *Mycobacterium tuberculosis* and 16S rRNA in human mitochondria, resulting in a narrow therapeutic index and uncertainty around dose optimization (9).

Putative pharmacokinetic targets for linezolid efficacy and toxicity have been proposed, based on *in vitro* infection models and small clinical studies. Previous work has shown that exposures may not be optimal for these targets at the current recommended linezolid dose (5, 10). Population-specific factors such as host genetics (11), HIV (8, 12), age (5, 13), creatinine clearance (10, 14), and body size (5, 15) may influence linezolid pharmacokinetic variability and pharmacodynamic effects, potentially leading to toxicity, treatment failure (16), and an increased risk of developing drug resistance (17). There are very limited pharmacokinetic data from HIV-positive patients, in whom linezolid-specific adverse events may be potentiated (9, 12, 18). Population pharmacokinetic models accurately determine causes of variability in drug exposure. These models can then be used for simulation of optimized dosing schedules that balance efficacy and toxicity (19). We aimed to characterize the population pharmacokinetic of linezolid in South African DR-TB patients with a high prevalence of HIV and estimate the probability of efficacy and toxicity target attainment from simulations of different dosing regimens.

RESULTS

Demographics and clinical profile. A total of 124 participants provided pharmacokinetic data, including 30 who were intensively sampled, contributing a total of 444 observations over a 6-month dosing period. Initially, 116 patients were receiving 600 mg daily, and 19 patients had their dose reduced to 300 mg (11 participants were sampled at both doses). Of the 30 patients in the intensive pharmacokinetic visit only 4 were dosed 300 mg daily. The baseline characteristics of the patients are shown in Table 1; more than half the participants were HIV positive.

MIC data Fig. 1 were available for isolates from 83 participants (Fig. 1). All isolates had MIC $\leq$ 1.0 mg/liter and 77% had an MIC of 0.5 mg/liter. There was no apparent association between linezolid MIC level and degree of drug resistance.

Population pharmacokinetic model. Linezolid pharmacokinetics was best described by one-compartment disposition kinetics with linear elimination and a first-order absorption preceded by a series of transit compartments. All disposition parameters (central clearance and volume of distribution) were allometrically scaled by weight normalized to the median weight value observed in the cohorts (51 kg). There was no statistically significant association between creatinine clearance, age, sex, and HIV status and linezolid pharmacokinetic exposure (bioavailability and clearance). The typical value of clearance (CL/F) for the median patient was 3.57 liters/h (95% confidence interval [CI], 3.34 to 3.87), and central volume of distribution was 40.2 liters (38.2 to 42.9) (Table 2). Residual unexplained variability was best described by a combined additive and proportional error model. For nonobserved drug administration, a separate additive error was estimated, and we allowed an extra lag variability fixed to a standard deviation of $\pm$0.7 h relative to reported time of the dose (more details are provided in supplemental material). Values below the lower limit of quantification (LLOQ) were excluded from the data set (20). Only four points were below the limit of quantification, and all were predose samples. This was considered nonadherence, and the dosing records from the previous days were disregarded. A visual predictive check (VPC) showed adequate model fit in Fig. 2. Model-estimated secondary pharmacokinetic parameters, stratified by dose, are summarized in Table 3 and depicted in Fig. 3.

Probability of target attainment. At the standard 600-mg daily dose, linezolid achieved favorable probability of target attainment (PTA; 96%) for the efficacy target up to the

TABLE 1 Baseline participant characteristics

Variable[a]	(*n* = 124)
Age (yr)	33 (27.8 to 42)
Females, *n* (%)	61 (49.2)
Ethnicity, *n* (%)	
Black	92 (74.2)
Mixed race	30 (24.2)
White	2 (1.61)
Weight (kg)	56 (50 to 63.1)
Height (cm)	164 (157 to 168)
FFM (kg)	43.3 (36.7 to 48.4)
BMI (kg/m^2)	20.2 (18.2 to 23)
HIV positive, *n* (%)	71 (57.3)
M. tuberculosis resistance profile, *n* (%)	
MDR	9 (7.3)
Pre-XDR (Inj-R)	11 (8.9)
Pre-XDR (FQ-R)	32 (25.8)
XDR	72 (58.1)
Serum creatinine (μmol/l)	64 (53 to 75)[b]
Daily 300-mg dose, *n* (%)[c]	19 (14)

[a]Data are expressed as median (IQR) or number (percent). BMI, body mass index; FFM, fat-free mass; ART, antiretroviral therapy; Inj-R, injectable-resistant; FQ-R, fluoroquinolone-resistant.
[b]Data were missing for 10 participants.
[c]Eleven patients had their dose reduced to 300 mg upon experiencing linezolid-related adverse events in addition to eight patients who were initially started on a 300-mg daily dose.

MIC value of 0.5 mg/liter; this dropped to 55% at the critical concentration of 1 mg/liter. Daily 1,200-mg dosing achieved 96% PTA up to MIC 1 mg/liter. The 300-mg dose did not achieve adequate PTA above MIC values of 0.25 mg/liter (Fig. 4). For toxicity targets, the standard 600-mg daily dose exceeded the 2- and 7-mg/liter targets for C_{min} in 54 and 2.2%, respectively; the probabilities of exceeding these targets at 1,200-mg dosing were 82.2 and 23.1%, respectively. Daily 300-mg dosing had a 16.5% chance of exceeding 2 mg/liter and was predicted not to exceed 7 mg/liter (Fig. 5). The cumulative fraction of response (CFR) for 300-mg daily was predicted to be 45%; for the standard 600-mg daily dose, the CFR reached 87 and 98% for the 1,200-mg daily dose.

DISCUSSION

We characterized the population pharmacokinetics of linezolid in South African patients with drug-resistant tuberculosis and demonstrated that the standard 600-mg dose is likely

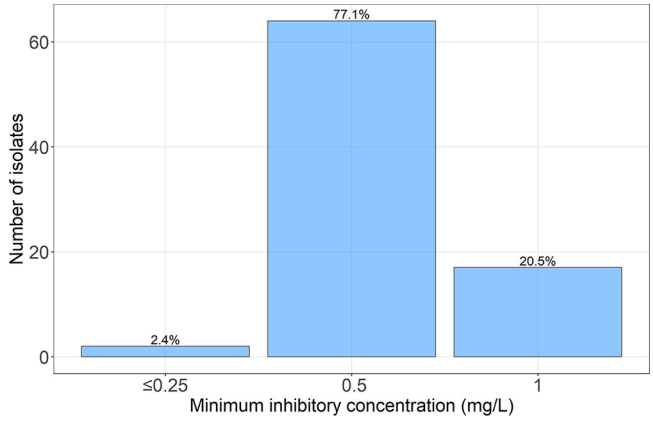

FIG 1 Distribution of *M. tuberculosis* MICs for linezolid done on cultured isolates taken before the start of tuberculosis treatment.

TABLE 2 Final population pharmacokinetic model parameters

Parameter description	Typical value (95% CI)[a]
Clearance (l/h)[b]	3.57 (3.34 to 3.87)
Central volume of distribution, V_c (l)[b]	40.2 (38.2 to 42.9)
Absorption mean transit time (h)	0.528 (0.36 to 0.687)
No. of transit compartments	5 (fixed)
Absorption rate constant, K_a (1/h)	1.22 (0.933 to 1.69)
Bioavailability, F	1 (fixed)
Proportional error (%)	9.53 (8.42 to 11.1)
Additive error (mg/liter)[c]	
Observed dosing	0.05 (fixed)
Unobserved dosing	0.651 (0.461 to 0.928)
Between-subject variability (%)[d]	
Clearance	37.1 (30.3 to 43.1)
Between-occasion variability (%)[d]	
Absorption mean transit time	56.8 (49.6 to 66.2)
Absorption rate constant	78.5 (54.7 to 100)
Bioavailability	22.0 (17.2 to 26.9)

[a]95% confidence intervals obtained with sampling importance resampling technique using PsN software.
[b]Allometric scaling used for CL, V_c; typical values reported for typical median patient with 56 kg weight.
[c]The estimate of this additive error was not statistically significant from its lower bound (LLOQ/2); thus, it was fixed to that value.
[d]Between-subject variability and between-occasion variability were assumed to be log-normally distributed and reported as approximate (%CV).

to achieve *in vitro* efficacy targets at the most frequent MIC values, but the 300-mg dose had a low probability of efficacy target attainment. Importantly, HIV coinfection had no effect on linezolid PK parameters. More than half the patients were estimated to exceed putative toxicity targets at the standard 600-mg daily dose, indicating that linezolid has a narrow therapeutic index in tuberculosis.

The value of CL estimated in our population, 3.57 liters/h, was lower than previously reported CL values ranging from 7.5 to 9.96 liters/h in model-based analyses from tuberculosis patients (10, 21–23). In previous analyses involving non-TB patients or healthy volunteers, the clearance value ranged from 2.06 to 13.5 liters/h (13, 15, 24–30). Possible explanations for the large variability of clearance in different studies include differing weight distributions across populations and various durations of linezolid exposure (linezolid may inhibit its own metabolism) (25). Additionally, none of the reported models accounted for interoccasion variability in absorption or bioavailability parameters, which could introduce bias on PK parameter estimates (31, 32).

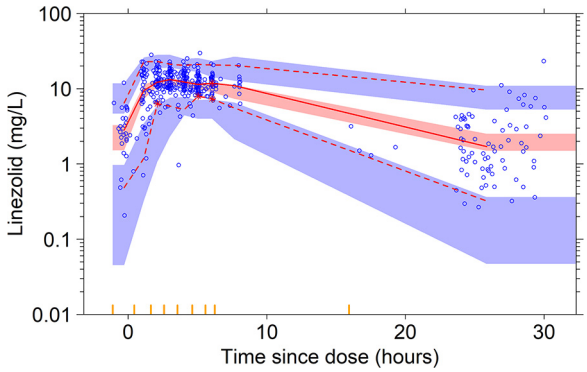

FIG 2 Prediction-corrected visual predictive check (PcVPC) for linezolid concentration versus time (time since dose). Circles represent original data; the dashed and solid lines are the 5th, 50th, and 95th percentiles of the original data, while the shaded areas are the corresponding 95% confidence intervals for the same percentiles, as predicted by the model. The vertical yellow lines on the *x* axis represent bins for sampling time points. An appropriate model is expected to have most observed percentiles within the simulated confidence intervals.

TABLE 3 Summary of model-derived pharmacokinetic (PK) parameters and predicted target attainment stratified by dose level for patients in the current study

Variable[a]	300 mg (*n* = 19)	600 mg (*n* = 116)	Total (*n* = 135)
C_{24h} (mg/liter)	1.16 (0.87 to 1.66)	1.98 (1.41 to 2.47)	1.92 (1.28 to 2.29)
AUC_{0-24h} (mg·h/liter)	92.3 (67.1 to 101)	159 (132 to 186)	151 (122 to 183)
$fAUC_{0-24h}$/MIC > 119 MIC = 0.5 mg/liter	10 of 19	115 of 116	125 of 135
$fAUC_{0-24h}$/MIC > 119 MIC = 1 mg/liter	0 of 19	51 of 116	51 of 135
C_{24h} > 2 mg/liter	3 of 19	56 of 116	59 of 135

[a]The data are presented as medians (IQR). AUC_{0-24}, area under the 24-h concentration-time curve.

However, the estimated value of the central volume of distribution in our analysis, 40.2 liters, was similar to those previously reported in TB patients: median (IQR) of 40.6 (36.3 to 57.4) (10, 21–23, 33–35). Our parameter estimates are comparable with those from a previously reported noncompartmental analysis of the same data (5) and those from other populations (33).

Almost all patients in the current study receiving standard 600-mg daily dosing had exposure values exceeding the efficacy target (*n* = 115/116), and a large proportion (*n* = 56/116) had trough concentrations exceeding the safety threshold. For patients receiving 300 mg, around 50% (10 of 19) achieved exposure values above the efficacy target, and only 3 of 19 had trough concentrations below the toxicity threshold. This highlights the need for continued toxicity monitoring, even after dose reduction. In contrast to other pharmacokinetic studies in tuberculosis, we did not find a significant effect of age and creatinine clearance on linezolid exposure (5, 10). There was also no impact of HIV infection on linezolid pharmacokinetics in our population. Two small studies have suggested that HIV may be a risk factor for linezolid-associated adverse events (8, 12). If this association is real, it is likely driven by pharmacodynamic effects in HIV rather than increased drug exposure (5).

Because of linezolid's narrow therapeutic window and dose-dependent toxicity, it is important to identify the lowest effective dose in tuberculosis treatment, but this has been challenging in single-arm cohort studies. Although excellent treatment outcomes were observed with linezolid use at 1,200 mg daily in the Nix-TB trial, a substantial number of patients experienced treatment-limiting adverse events (36). In contrast, a small Korean study demonstrated favorable treatment outcomes with a 4-fold lower dose of 300 mg daily, but over a quarter of patients still suffered linezolid-related toxicity (37). Therapeutic drug monitoring (TDM) has been proposed as a strategy for linezolid optimization in tuberculosis therapy (38, 39) because of low within-person variability, stability on dried blood spots (40), and use of limited sampling strategy (21). However, clinical studies are need to better define exposure targets for toxicity (and efficacy) prior to implementation of TDM.

Our simulations showed that a total daily dose of 300 mg would achieve an *in vitro*-

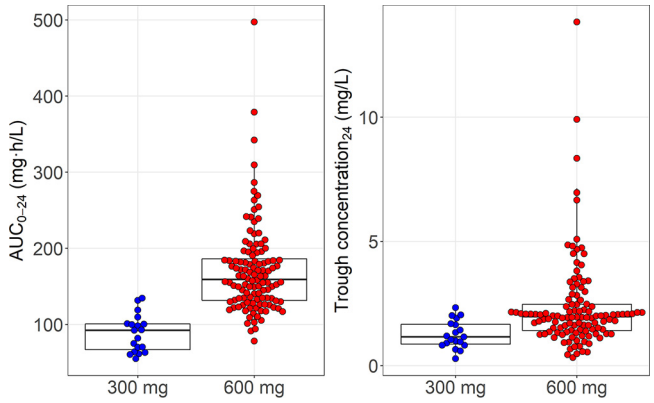

FIG 3 Box and whisker plots showing secondary model-derived exposure parameters, stratified by dose. The dots represent individual values; whiskers are 2.5th and 97.5th percentiles. *n* = 19 for 300 mg and 116 for 600 mg. AUC_{0-24}, area under the concentration-time curve from 0 to 24 h.

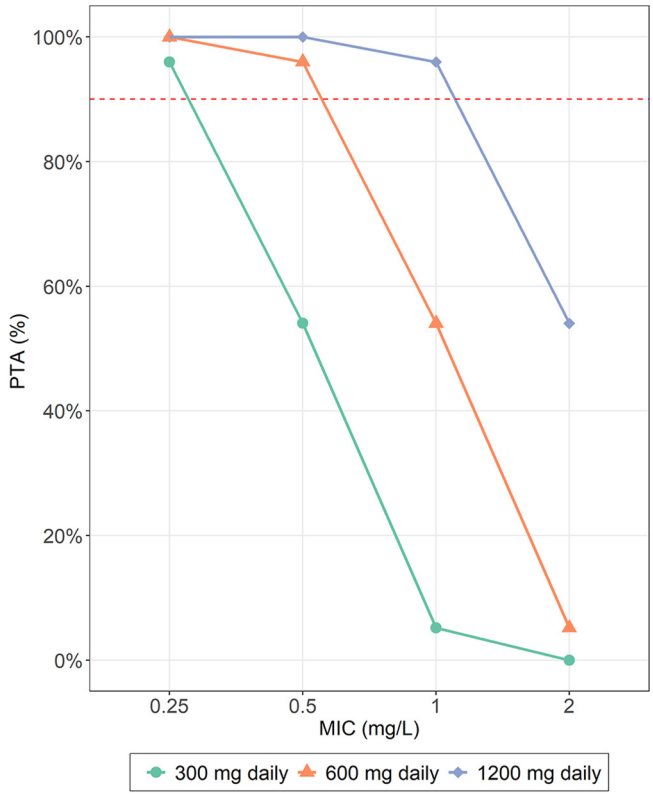

FIG 4 PTA of efficacy (area under the concentration-time curve for the free, unbound fraction of the drug [*f*AUC]/MIC > 119) for the three simulated linezolid dosage regimens versus MIC distributions.

derived efficacy target with 90% probability only up to an MIC of 0.25 mg/liter, which was found in less than 3% of isolates in our population. The efficacy target was achieved with 600- and 1,200-mg doses up to MIC values of 0.5 and 1 mg/liter, respectively, representing the range of wild-type *M. tuberculosis* isolates in the population. A recent population pharmacokinetic model based on data from HIV-negative tuberculosis patients generated slightly more conservative PTA predictions at published MIC values; this difference is explained by the much higher clearance observed in their population (6.32 liters/h) (10). Despite a high probability of achieving the efficacy target, the 600-mg dose had a 54% probability of exceeding the toxicity trough threshold of 2 mg/liter (compared with 17 and 82% for the 300- and 1,200-mg doses, respectively). A small study ($n = 9$) has shown that some patients may achieve putative PK/PD targets at the 300-mg dose, but this would need to be supported by therapeutic drug monitoring, which is unavailable in most high-tuberculosis-burden settings (41).

Our study has limitations. First, the sparse-sampling data relied on self-reported information on the time of the dose, which introduced uncertainty into the model. We mitigated this by estimating a separate, larger, residual error and allowing extra lag variability (fixed to a standard deviation of ±0.7 h) relative to the self-reported time of the dose. As shown in our VPC plots, the final model fitted the data adequately despite unobserved dosing. Second, the linezolid dose was reduced to 300 mg in a few patients due to the development of toxicity. This raises the possibility of channeling bias and an overestimate of exposure in this group resulting from intrinsically lower clearance. Third, the pharmacokinetic efficacy target was defined based on *in vitro* data (42, 43), which do not fully replicate disease in humans or closely mimic human kinetics (44) and have not been validated in clinical settings. Fourth, the safety threshold of 2 mg/liter is based on a small study involving 38 tuberculosis patients using a visually observed cutoff for any adverse events (45). The 7-mg/liter toxicity target relates to the development of thrombocytopenia in non-TB patients with short-term use; this complication occurs much less frequently in tuberculosis (36).

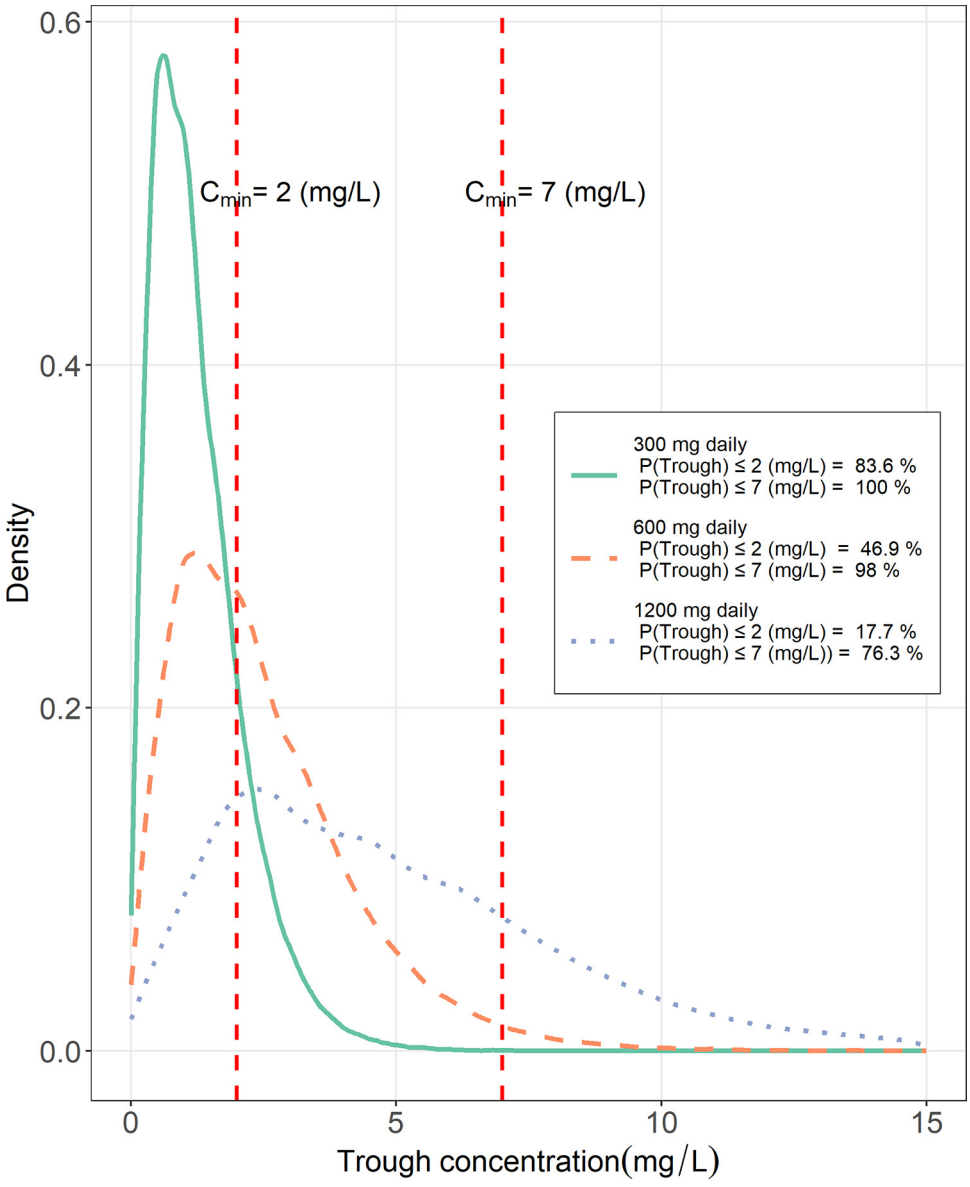

FIG 5 Probability density distributions for safety targets attainment following simulation of 300, 600, and 1,200 mg daily dosing of linezolid. The vertical lines on the *x* axis represent the experimentally derived safety threshold of 2 and 7 mg/liter.

Conclusions. We successfully developed a population PK model in South African patients with RR-TB, showing no effect of HIV or other important clinical covariates. We showed that standard dosing achieves putative efficacy targets but also exceeds putative toxicity targets, which supports close safety monitoring. Further studies are needed to define clinical PK/PD relationships in tuberculosis patients and to explore alternative dosing strategies (e.g., intermittent dosing or dosing for a shorter duration or weight-based dosing regimen) to optimize efficacy and minimize toxicity (46).

MATERIALS AND METHODS

Study population. Data were obtained from South African adults treated with linezolid-containing regimens for pulmonary DR-TB. Participants were enrolled into two studies: an observational cohort study (PROBeX) of patients with pre-XDR-TB (resistance to isoniazid and rifampin [MDR] plus additional fluoroquinolone or second-line injectable resistance) and XDR-TB (MDR with additional resistance to fluoroquinolones plus a second-line injectable agent) (47); and the intervention arm of an open-label clinical trial examining a shortened injection-free regimen for RR-TB (NExT; ClinicalTrials.gov NCT02454205) (5). Linezolid was administered as a 600-mg daily oral dose, which was reduced to 300 mg daily at the

discretion of local clinicians or trial staff in patients who developed toxicity. Subgroups of patients from both cohorts were consecutively enrolled in an intensive PK substudy; all patients in PROBeX underwent additional serial sparse pharmacokinetic sampling. The studies were approved by the institutional review boards at the University of Cape Town, Albert Einstein College of Medicine, and Emory University. All participants signed written informed consent.

Data sources. Clinical and laboratory data were collected monthly over 6 months for PROBeX participants; data from NExT participants were collected at study entry and during the intensive PK visit at month 2. The data included demographic and biometric information, HIV status, concomitant antituberculosis drugs and antiretroviral therapy (ART), and biochemical profile.

Plasma samples from participants in the intensive pharmacokinetic substudy were collected before dosing and at 1, 2, 3, 4, 5, 6, and 24 h postdose at month 2 after study enrollment. Some participants from PROBeX provided additional plasma samples at 8 and 48 h, as part of other study procedures. Linezolid was administered following a standardized meal and under the supervision of the study team. An additional plasma pharmacokinetic sample was collected at months 1, 2, and 6 after study entry for PROBeX participants following self-reported linezolid dosing times.

Linezolid concentrations were measured at the Division of Clinical Pharmacology at the University of Cape Town using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Using a deuterated internal standard, the LC-MS/MS method for linezolid was validated over a calibration range of 0.100 to 30 mg/liter. Over the period of sample analysis ($n = 8$ batches), a mean accuracy of 98.8% was achieved, with a mean precision of 5.93% (coefficient of variation [CV]) (48).

Model building and analysis. Pharmacokinetic data were analyzed with nonlinear mixed-effects modeling in NONMEM version 7.5 (ICON Development Solutions, Hanover, MD, USA) using an expectation maximization algorithm; we applied stochastic-approximation expectation maximization followed by important sampling to obtain objective function value for hypothesis testing. Pirana (Certara, Princeton, NJ, USA), Perl-speaks-NONMEM version 5.0 and Xpose4 (49) were used for NONMEM execution and postprocessing results. Final parameter estimates and 95% confidence intervals were obtained via the sampling-importance resampling procedure available in PsN (50). One- and two-compartment disposition kinetics with linear and nonlinear elimination were tested to describe the structural model of the linezolid. To describe the absorption process, we tested first-order absorption with and without lag, saturable absorption, and transit compartments absorption (51). Between-subject and -occasion random effects included on pharmacokinetic parameters were assumed to follow a lognormal distribution. Additive, proportional, and combined error models were tested to describe residual unexplained variability. Allometric scaling (52) was tested on all disposition parameters to account for the effect of body size with total body weight, fat mass, and fat-free mass (53) as body size descriptors. The effects of HIV status, age, creatinine clearance (estimated by Cockroft-Gault), and linezolid dose were investigated on clearance (CL), the volume of distribution (V_c), and bioavailability.

Model development and inclusion of covariates followed a stepwise approach based on physiological plausibility and improvement in model diagnostics. Model diagnostics included inspection of VPCs and the difference in the model objective function (ΔOFV), which was assumed to follow a chi-square distribution with a degree of freedom corresponding to the difference in the number of parameters between two nested models (ΔOFV of at least 3.84 points with $P < 0.05$).

Simulations. We used the final model parameter estimates to perform Monte Carlo simulations to evaluate the PTA. The selected targets were free AUC_{0-24}/MIC ($fAUC_{0-24h}$/MIC)>119, which represents an efficacy target of 80% maximal kill based on the hollow fiber infection model (10, 42, 54) and C_{min} values of >2 and >7 mg/liter, corresponding to thresholds for mitochondrial toxicity in TB patients and thrombocytopenia in patients with Gram-positive infection, respectively (45, 55).

We simulated exposure (C_{min} and AUC_{0-24}) following 300-, 600-, and 1,200-mg daily dosing, assuming steady state had been attained. To ensure the relevance of the simulations, we used demographic characteristics of TB patients obtained from pharmacokinetic studies conducted in West Africa and South Africa ($n = 1,000$) (56). Protein binding was assumed to be 30% (57). PTA was calculated as the proportion of simulated participants with PK exposure above the efficacy and toxicity targets.

Microbiological data. Baseline (pretreatment) *M. tuberculosis* isolates were retrieved from PROBeX participants. Linezolid MIC testing was performed on available isolates using the mycobacterial growth indicator tube system and continuous growth monitoring with Epicenter software. Dilutions ranged from 0.25 to 2 mg/liter based on published wild-type distributions and the suggested critical concentration of 1 mg/liter (58). The expected population probability of target attainment for a specific drug dose and a specific population of microorganisms (i.e., the CFR) (59) was calculated using the distribution of observed MICs in our cohort for the different simulated dosing regimens. The simulation was performed in NONMEM 7.5, and postprocessing of the results was performed in R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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